

REMARKS

Reconsideration of the rejections set forth in the Office action mailed July 1, 2004 is respectfully requested. Claims 8-14 were cancelled in the response to restriction requirement filed July 2, 2003, and claim 5 was cancelled with the previous response. Claims 1-4, 6-7 and 15-16 are currently pending.

I. Amendments

Amendments to clause (a) of claim 1 find support in previous claim 4 (length of words) and in the Abstract (tag precursor "consists of" one or more words).

Claim 1 is further amended for clarity and to more particularly point out the features of the methods shown in the embodiments of Figures 1-2 in the specification.

In particular, the subject matter of paragraphs (b), (c) and (d) of amended claim 1 finds support in Figures 1A, 1B and 2 and the corresponding description in the specification, as follows.

With reference to the embodiment of Fig. 1A, the specification teaches, at page 11, line 31 to page 12, line 1:

Cycles of word addition in the preferred embodiment, illustrated in FIG. 1a, begin with the step of cleaving (122) vector (121) with r1 and r2, to remove **segment (123)**, thereby leaving **opened vector (124)**, which is then isolated using conventional protocols. In this embodiment, r2 cleaves the oligonucleotide tag precursor at the upstream-most word of the tag. **Separately**, restriction endonucleases r1 and r3 recognizing restriction sites (104) and (110), respectively, are used to cleave (116) vector (100) **to produce fragment (118)**, which is **inserted (126) into opened vector (124)** to form vector (128), **thereby elongating the oligonucleotide tag precursors by two words**.

As shown in Fig. 1A, fragment (123), the "first fragment", contains "at most one word" (in this case, no words), and the "second fragment" (118), which contains "one or more words", is inserted into opened vector (124), the "first opened amplicon", which elongates the tag precursors in that vector.

With reference to the embodiment of Fig. 1B, the specification teaches, at page 12, lines 12-16:

In aliquot (160), vector (150) is digested with r1 and r2 so that fragment (161) is excised and opened vector (166) is formed. Separately, in aliquot (162), vector (150) is digested with r1 and r3 so that 2-word fragment (164) is excised. After purification, 2-word fragment (164) is inserted and ligated (168) into opened vector (166) to form vector (170), which contains oligonucleotide tag precursors consisting of four words each.

As shown in Fig. 1B, and described above, fragment (161), the "first fragment", contains "at most one word" (in this case, no words). The "second fragment" (164), which contains "one or more words", is inserted into opened vector (166), the "first opened amplicon", which elongates the tag precursors in that vector.

With reference to the embodiment of Fig. 2, the specification teaches, at page 13, line 21 to page 14, line 3:

Vector (221), which may be a sample of starting vector (200) or a previously processed vector, is cleaved (224) with r4 and r6 to produce fragment (225) and opened vector (228), which is isolated using conventional protocols... Separately, a sample of vector (200) is cleaved (222) with r4 and r8 to produce fragment (218), which is isolated.... **Fragment (218) is combined with opened vector (228) under conditions that permit the single stranded forms of the words (220) and (226) to form perfectly matched duplexes... After insertion and ligation (230), vector (232) is formed which contains an elongated oligonucleotide tag precursor.**

As shown in Fig. 2, and described above, fragment (225), the "first fragment", contains at most one word (in this case, one single stranded word (226)). The "second fragment" (218), which contains "one or more words", is inserted into opened vector (228), the "first opened amplicon", to produce elongated tag precursors in that vector.

The subject matter of amended claim 4 finds support in the specification at page 7, lines 22-24 and at page 7, line 24 to the bottom of the page.

Claim 15 has been amended to recite a repertoire of oligonucleotide tag precursors, as described in the specification at page 7, lines 8-20.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, Second Paragraph

The pending claims 1-7 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in view of the Examiner's continued assertion that the terms "word" and "minimally cross-hybridizing" are indefinite.

(Items 3-6.) The Examiner asserts that the patents which are incorporated by reference (US 5,604,097 and its CIP, serial no. 08/659,453, which issued as US 5,846,719) rarely contain the term "word" and the term "minimally cross-hybridizing" in the same paragraph. While this may be the case, the applicants do not see how this finding impugns the entire disclosures of these patents, which describe the concept of oligonucleotide tags made up of words, which may also be called "subunits" (see e.g. col 6, line 14 of the '097 patent), selected from minimally cross-hybridizing sets, in detail. See, for example, col 3, lines 12-32; col 6, line 11 to col 9, line 21; and Appendix I of the '097 patent.

Even without the disclosure of the incorporated references, the present specification clearly defines these concepts as well, as pointed out in the previous response. See, for example, page 2, lines 17-29; page 4, lines 28-34; and page 7, line 21 to page 9, line 2.

(Item 7.) In view of the additional definitions of the terms "complement", "perfectly matched", and "mismatch" at page 4, lines 1-9 and page 4, line 27 to page 5, line 2, which discuss triplex as well as duplex structures, the applicants believe that one skilled in the art would be able to apply the concept of a minimum number of mismatches to triplex as well as duplex structures.

(Item 8.) The claim phrase at issue is "a duplex consisting of a word of the set and the complement of any other word of the set contains a number of mismatches...".

The duplex does not consist of "a word of the set" in isolation, as implied by the Examiner; rather, "a word of the set" and "the complement of any other word of the set" together make up

the "duplex". The meaning of the phrase should be clear from the use of the singular verb "contains" referring to "duplex".

III. Rejections under 35 U.S.C. §112, First Paragraph

The pending claims were rejected under 35 U.S.C. §112, first paragraph, as being directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

(Item 12.) The Examiner again asserts that the "repertoire of oligonucleotide tags" "can be of virtually any length and nucleotide composition". However, as noted in the previous response, independent claim 1 specifies that the tags have "a predetermined length in the range of from 18 to 60 nucleotides". Independent claim 15 specifies the range of length and number of possible repetitions of every element in the claimed formula, so it is a simple matter of arithmetic to determine the range of lengths of the oligonucleotide tags.

(Item 13.) The Examiner again asserts, with respect to the description of "minimally cross hybridizing sets", that the cited documents "have been improperly incorporated by reference". This issue was addressed at great length in the previous response, and that discussion will not be repeated here. As noted above (Items 3-6), the present specification in itself provides a description of this concept that would be clear to one skilled in the art.

The following is reproduced from the previous response:

"The applicants also disclose that preferred sets of tags include those whose perfectly matched duplexes have approximately equal stability, and refer to published sources of methods of determining duplex stability (page 9, second full paragraph). The Examiner contends that these embodiments are not adequately described. However, the MPEP, in its description of determining adequacy of written description, cites case law in stating that "Information which is well known in the art need not be described in detail in the specification" (8th ed., Rev. 2, page 2100-170) and that "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. ... If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met" (8th

ed., Rev. 2, page 2100-172). The applicants contend that one of skill in the art at the time of filing the application would have been familiar with the variables involved in duplex stability.

The decision of *University of California v. Eli Lilly and Co.*, cited in the Office Action (page 6), found that the disclosure of an amino acid sequence did not provide adequate written description to support a claim directed to a DNA encoding that sequence. Because the sequence of the claimed DNA was presumably not "conventional or well known to one of ordinary skill in the art" at the time of filing of that application, this case does not appear to be pertinent to the instant application."

The Examiner responds (Item 19) that "there is no evidence of record that establishes what is known in the art". It would appear to the applicant that a series of published papers, such as the "published sources of methods of determining duplex stability (page 9, second full paragraph)", would on its face be subject matter known in the art.

(Items 14/15.) As noted above, independent claim 15 has been amended to recite a repertoire of oligonucleotide tags and no longer recites a cloning vector.

In view of the foregoing, the applicants submit that the pending claims comply with the written description requirements of 35 U.S.C. §112, first paragraph.

IV. Further Rejections under 35 U.S.C. §112, First Paragraph

The pending claims were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation.

At Item 22, the Examiner again asserts that the repertoire of oligonucleotides "can be of virtually any length". This statement is refuted by the clear language of the claims, as noted above.

The Examiner asserts, once again (Item 21), that "Disclosures critical to enabling the claimed method are not properly incorporated by reference". As discussed in great detail in the previous response, the applicants do not agree that these references are "critical to enabling the claimed method; nor are they "not properly incorporated by reference". Moreover, even if these references were not incorporated into the present disclosure, their content was still available to one skilled in the art at the time of filing of the application.

To reiterate, the independent claim includes the steps of:

- (a) providing a repertoire of same-length oligonucleotide tag precursors in an amplicon, wherein each oligonucleotide tag precursor consists of one or more words, and each word is an oligonucleotide having a length of three to fourteen nucleotides, selected from a minimally cross-hybridizing set of oligonucleotides, such that a duplex consisting of a word of the set and the complement of any other word of the set contains a number of mismatches that is either 1, 2 or 3 less than the length, in nucleotides, of the word;
- (b) cleaving a first aliquot of the amplicon to produce a first opened amplicon and a first fragment, said fragment containing at most one word from said oligonucleotide tag precursor;
- (c) cleaving a second aliquot of the amplicon to produce a second opened amplicon and a second fragment, said fragment containing one or more words from said oligonucleotide tag precursor;
- (d) ligating said second fragment containing one or more words into said first opened amplicon, thereby elongating said oligonucleotide tag precursors in said first aliquot of the amplicon;
- (e) amplifying the elongated oligonucleotide tag precursors in said first aliquot of the amplicon; and
- (f) repeating steps (b) through (e) until a repertoire of oligonucleotide tags having the predetermined length is formed.

The Examiner asserts that the specification does not enable one to make and use the claimed oligonucleotides and vectors (Items 23-24). Thus, the Examiner implies that, in spite of the teachings of the current specification, and the general knowledge in the field regarding oligonucleotide synthesis, restriction enzymes, ligation, cloning, amplification, etc., one skilled in the art would not have been able to carry out the claimed steps.

As stated in *In re Marzocchi and Horton*, 439 F2d 220, 169 USPQ 367 (CCPA 1971), "Specification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding in scope to those used in describing and defining subject matter sought to be patented *must* be taken as in compliance with enabling requirement of first paragraph of 35 U.S.C. §112 *unless* there is a reason to doubt objective truth of statements contained therein which must be relied on for enabling support.. it is incumbent upon Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts truth or accuracy of statement in

supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with contested statement; otherwise, there would be no need for applicant to support his presumptively accurate disclosure."

The Examiner has provided no evidence supporting his assertion that one skilled in the art would not have been able to carry out and use the claimed invention, beyond clearly inaccurate statements such as the assertion that the oligonucleotide tag precursors "can be of virtually any length".

In view of the foregoing, the applicants submit that the pending claims comply with the enablement requirements of 35 U.S.C. §112, first paragraph.

V. Rejections under 35 U.S.C. §102(b)

The rejection of claims 15-16 under 35 U.S.C. §102(b), as being anticipated by Stratagene Cloning Systems (1993, page 27), was reiterated. This rejection is traversed for the following reasons.

The Examiner repeats his assertion (Item 30) that "x₁ through x_{n-1} can be 0" in the formula of claim 15, despite the clear language of the claim, emphasized in boldface in the previous response, that "**at least one of x₁ through x_{n-1} is 1 or 2**". Therefore, the formula w₁w₂w₃w₄ postulated by the Examiner is **not** a possible embodiment of the claim. As stated in the previous response, in the oligonucleotide tags shown in the claim, "**at least two words...are separated by one or two nucleotides**" (page 4, lines 6-7).

Such repeated discounting of the clear language of the claim does not promote efficient prosecution.

As pointed out in the previous response, there is no evidence in the cited reference that the oligonucleotides contained in the vectors therein have the claimed structural features (i.e., where "each of w₁ through w_n is a word consisting of an oligonucleotide having a length from three to fourteen nucleotides...selected from a minimally cross hybridizing set, wherein a word of the set and a complement of any other word of the set has a number of mismatches that is either 1, 2 or 3 less than the length of the word"; and where "at least one of x₁ through x_{n-1} is 1 or 2", such that at least two words are separated by one or two nucleotides).

Accordingly, the applicants request that the rejection be withdrawn.

VI. Conclusion

In view of the foregoing, the applicants submit that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,



LeeAnn Gorthey
Registration No. 37,337

Correspondence Address:

PAYOR NUMBER 22918

PHONE: (650) 838-4403

FAX: (650) 838-4350